534 Rec'd PCT/PTO 22 AUG 2000

BOX PCT

ATTORNEY'S DOCKET NO: 24356

U.S. DEPARTMENT OF COMMERCE, PATENT AND TRADEMARK OFFICE		DATE: 22 August 2000 (22.08.2000)
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLN. NO. (if known): Not Yet Assigned 09/622719
INTERNATIONAL APPLICATION NO.: ~~PCT/EP99/02591~~	INTERNATIONAL FILING DATE: 23 February 1999 (23 02.99)	PRIORITY DATE CLAIMED: 23 February 1998 (23.02.98)

TITLE OF INVENTION: METHOD FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR

APPLICANT(S) FOR DO/EO/US: LOWENHEIM, Hubert

Applicant hereby submits to the Unites States Designated/Elected Office (DO/EO/US) the following items and other information:

1. X This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. __ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. X This express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).

4. X A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. X A copy of the International Application as filed (35 U.S.C. 371(c)(2)):

   a. X is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ___ has been transmitted by the International Bureau.
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. X A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. X Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))

   a. __ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. __ have been transmitted by the International Bureau.
   c. __ have not been made; however, the time limit for making such amendments has NOT expired.
   d. X have not been made and will not be made.

8. __ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ___ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. X A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

ITEMS 11. TO 16. BELOW CONCERN OTHER DOCUMENT(S) OR INFORMATION INCLUDED:

11. __ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. __ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. X A **FIRST** preliminary amendment.
    _ A **SECOND** or **SUBSEQUENT** preliminary amendment

14. __ A substitute specification.

15. __ A change of power of attorney and/or address letter.

16. X TRANSMITTAL FORM; FEE CALCULATION; INTERNATIONAL PUBLICATION WO 99/43088; INTERNATIONAL PUBLICATION DATE 26 AUGUST 1999; VERIFIED ENGLISH LANGUAGE TRANSLATION OF APPLICATION CONSISTING OF 14 PAGES INCLUDING; 9 PAGES TEXTUAL SPECIFICATION, 3 PAGES OF 29 CLAIMS; 1 PAGE CONTAINING THE ABSTRACT; 1 SHEETS DRAWINGS; PCT/ISA/210 INTERNATIONAL SEARCH REPORT; VERIFIDED ENGLISH TRANSLATION OF THE CLAIMS (1 TO 27) AS AMENDED DURING THE INTERNATIONAL PRELIMINARY EXAMINATION; PRELIMINARY AMENDMENT TO BE EXAMINED; UNEXECUTED INVENTOR'S DECLARATION; PCT/IPEA/416 NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT; PCT/IPEA/409 INTERNATIONAL PRELIMINARY EXAMINATION REPORT; PCT/RO/101 REQUEST; PCT/IB/304 NOTIFICATION CONCERNING SUBMISSION OF PRIORITY DOCUMENT; PCT/IB/332 INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION; PCT/IPEA/402 NOTIFICATION OF RECEIPT OF DEMAND.

534 Rec'd PCT/PTO 22 AUG 2000

ATTORNEY'S DOCKET NO: 24356

U.S. APPLICATION NO. (if known)	INTERNATIONAL APPLICATION NO.	DATE: 17 August 2000 (17.08.2000)
09/622719	PCT/EP99/01153	

17. x The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO:.....$840.00	$ 840.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$760.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00		
International preliminary examination fee (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$ 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$ 840.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NO. FILED	NO. EXTRA	RATE		
TOTAL	34 -20=	14	X $ 18.00	$	**252.00**
INDEPENDENT	5 - 3=	2	X $ 78.00	$	156.00
Multiple dependent claims(s) (if applicable)			+ $260.00	$	0.00
TOTAL OF ABOVE CALCULATIONS =				$	**408.00**
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	**0.00**
SUBTOTAL =				$	1,248.00
Processing fee of **$130.00** for furnishing the English translation later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	0.00
TOTAL NATIONAL FEE =				$	1,248.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00 per property +**				$	**0.00**
TOTAL FEES ENCLOSED =				$	**1,248.00**
				Amount to be: refunded	$
				charged	$

#3

A 35 223 PCT/US Atty. Docket No. 24356

Applicant/Patentee: Hubert LOEWENHEIM
Serial/Patent No.: 09/622,719 Atty. Dkt No. 24356
Filed on/Issued on: 22 August 2000
For: Method for the treatment of diseases or disorders of the inner ear

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR § 1.9(f) AND § 1.27(b)) - SMALL BUSINESS CONCERN

I hereby declare that I am:
[ ] The owner of the small business concern identified below:
[x] An official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN Otogene Aktiengesellschaft
ADDRESS OF CONCERN Vor dem Kreuzberg 17, D-72070 Tuebingen, Germany

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR § 121.8-18, and reproduced in 37 CFR § 1.9(d), for purposes of paying reduced fees under 35 USC § 41(a) and (b), in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement: (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that the rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention entitled Method for the treatment of diseases or dis- by inventor(s) Hubert LOEWENHEIM described in: orders of the inner ear

[x] The specification filed herewith
[ ] U.S. Application Serial No 09/622,719 filed August 22, 2000
[ ] U.S. Patent No. _____, issued _____

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR § 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR § 1.9(d) or a non-profit organization under 37 CFR § 1.9(e).

FULL NAME _____

ADDRESS _____

[ ] Individual [ ] Small Business [ ] Non-Profit

NOTE: Separate Verified Statements are required from each named person, concern or organization having rights to the invention averring their status as small entities (37 CFR § 1.27).

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the Issue Fee or any maintenance fee due after the date on which status as small entity is no longer appropriate (37 CFR § 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC § 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this Verified Statement is directed.

NAME OF PERSON SIGNING ~~Dr. Hubert Löwenheim~~ Dr. Christof Antz
TITLE OF PERSON SIGNING ~~Scientific Advisor~~ Dir. of Research and Development
ADDRESS OF PERSON SIGNING ~~Philipp von Heck Str.~~ Schwärzlocher Str. 60
~~72076 Tübingen~~ 72070 Tübingen
Signature _____ Date 23.08.2000

534 Rec'd PCT/PTO 22 AUG 2000

ATTORNEY'S DOCKET NO: 24356

U.S. APPLICATION NO. (if known) 09/622719	INTERNATIONAL APPLICATION NO. PCT/EP99/01153	DATE: 22 August 2000 (22.08.2000)

a. X One check in the amount of $1,248.00 to cover the above fees is enclosed.

b. __ Please charge my Deposit Account No. 14-0112 in the amount of $_____ to cover the above fees. (A duplicate copy of this sheet is enclosed.)

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0112.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed to request that the application be restored to pending status.

Send All Correspondence To:

Gary M. Nath
NATH & ASSOCIATES PLLC
1030 15th Street, N.W.
Sixth Floor
Washington, D.C. 20005

(202) 775-8383 (phone)
(202) 775-8396 (fax)

GARY M. NATH
Registration Number 26,965
JERALD L. MEYER
Registration Number 41,194

Rev. 02/98

422 Rec'd PCT/PTO 22 AUG 2000

Attorney Docket No. 24356

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

09/622719

PATENT & TRADEMARK OFFICE AUG 22 2000 JC91

In re Application of:
LOWENHEIM, Hubert
International Application No. PCT/EP99/01153
Serial No. NOT YET ASSIGNED
International Filing Date: 23 February 1999 (23.02.99)
Filed: August 22, 2000
For: **METHOD FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR**

TRANSMITTAL LETTER

The Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith for filing in the U.S. Patent and Trademark Office is the following:

(1) Transmittal Letter
(2) Transmittal Letter To U.S. Designated/Elected Office (DO/EO/US) Concerning Filing under 35 U.S.C. 371
(3) International Publication No: WO 99/42088
International Publication Date: 26 August 1999 (26.08.99)
with English translation consisting of 14 pages including:
9 pages Textual Specification
3 Pages of 29 claims
1 Sheet of Drawings (1 figure)
(4) PCT/ISA/210 International Search Report
(5) Verified English translation of the claims (1 to 27) as amended during the International Preliminary Examination
(6) Preliminary Amendment to be examined
(7) Unexecuted Inventor's Declaration
(8) PCT/IPEA/416 Notification of Transmittal of International Preliminary Examination Report
(9) PCT/IPEA/409 International Preliminary Examination Report
(10) PCT/RO/101 Request
(11) PCT/IB/304 Notification Concerning Submission of Priority Document
(12) PCT/IB/332 Information Concerning Elected Offices Notified of Their Election
(13) PCT/IPEA/402 Notification of Receipt of Demand
(14) Check No. 13292 $ 1,248.00 for Government Filing Fee and additional claims fee
(15) Postcard for early notification of serial number.

Respectfully submitted,
NATH & ASSOCIATES PLLC

By: _____
Gary M. Nath
Registration No. 26,965
Jerald L. Meyer
Registration No. 41,194

Date: August 22, 2000
NATH & ASSOCIATES PLLC
1030th 15TH Street, NW - 6th Floor
Washington, D.C. 20005
GMN/JLM/dd:PCTappl.trans

TO 1 2 9 9 7 1 0 #3

BOX PCT-REFUND REQUEST
Attorney Docket No. 24356

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
LOWENHEIM, Hubert
International Application No. PCT/EP99/01153
Serial No. 09/622,719
International Filing Date: 23 February 1999 (23.02.99)
Filed: August 22, 2000
For: **METHOD FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR**

REQUEST FOR REFUND

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This request for refund is made for the amount of $624.00 which is half of the originally paid Government Filing Fee for the captioned application.

A Filing Fee of $1,248.00 was paid on August 22, 2000 for the filing fee and additional claims fee. A Verified Statement Claiming Small Entity Status for the applicant is being filed concurrently with this Request for a Refund and Completion of Filing Requirement. This request and the Verified Statement Claiming Small Entity Status are being filed before the two-month time limit of October 22, 2000, to claim a refund. We enclose copies of the Small Entity Statement along with a copy of Check No. 13292 for $1,248.00 and the stamped filing receipt and postcard, showing payment of the Government Filing Fee on August 22, 2000.

Please credit the refund of the overpayment to our Deposit Account No. 14-0112.

Respectfully submitted,
NATH & ASSOCIATES PLLC

Gary M. Nath
Registration No. 26,965
Customer No. 20529

Date: October_____, 2000
NATH & ASSOCIATES PLLC
1030 15th Street, N.W., 6th Floor
Washington, D.C. 20005
(202) 775-8383
GMN/dd:REFUND.reqPCT

09/622719
534 Rec'd PCT/PTO 22 AUG 2000

BOX PCT
Attorney Docket No. 24356

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
LOWENHEIM, Hubert
International Application No. PCT/EP99/01153
Serial No. NOT YET ASSIGNED
International Filing Date: 23 February 1999 (23.02.99)
Filed: August_____, 2000
For: **METHOD FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR**

PRELIMINARY AMENDMENT

The Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Before calculating the filing fee for the above identified application, please enter the following amendments:

IN THE CLAIMS:

Please cancel the Article 34 amended claims 1-27 and submit the following new set of claims without prejudice.

28. Process for the treatment of diseases or disorders of the inner ear linked with damage or destruction of the sensory cells of the inner ear, characterized in that for the regeneration of the sensory cells of the inner ear the inhibiting action of at least one cell cycle inhibitor present in the inner ear is at least partly inhibited or eliminated by an active ingredient.

29. Method of treating diseases or disorders of the inner ear linked with damage or destruction of the sensory cells of the inner ear by administering an active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear.

30. Method of preparing a pharmaceutical composition or a medicament for the treatment of diseases or disorders of the inner ear linked with damage or destruction of the sensory cells of the inner ear by administering an active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear.

31. Process according to claim 28, characterized in that the regeneration of the sensory cells of the inner ear takes place by stimulating proliferation of the supporting cells of the inner ear.

32. Process according to claim 28, characterized in that the sensory cells of the inner ear are hair sensor cells.

33. Process according to claim 28, characterized in that the cell cycle inhibitor is a cyclin-dependent kinase inhibitor.

34. Process according to claim 33, characterized in that the cyclin-dependent kinase inhibitor is the cyclin-dependent kinase inhibitor $p27^{kip1}$.

35. Process according to claim 28, characterized in that the disease or disorder of the inner ear is a perceptive deafness.

36. Process according to claim 28, characterized in that the active ingredient is a least one peptide or at least one protein.

37. Process according to claim 28, characterized in that the active ingredient is at least one nucleic acid molecule.

38. Process according to claim 37, characterized in that the nucleic acid molecule codes for a peptide or a protein.

39. Process according to claim 37, characterized in that the nucleic acid molecule is a DNA molecule.

40. Process according to claim 39, characterized in that the nucleic acid molecule is a cDNA molecule.

41. Process according to claim 37, characterized in that the nucleic acid molecule is a RNA molecule.

42. Process according to claim 28, characterized in that the active ingredient is in the form of a vector.

43. Process according to claim 42, characterized in that the vector is a viral vector.

44. Process according to claim 43, characterized in that the virus is a retrovirus, an adenovirus or an adeno-associated virus.

45. Process according to claim 42, characterized in that the vector is a non-viral vector.

46. Process according to claim 37, characterized in that it is a nucleic acid molecule packed in a liposome or a lipoplex.

47. Process according to claim 28, characterized in that the active ingredient is used in a therapeutically active quantity.

48. Process according to claim 28, characterized in that the active ingredient is intended for local application.

49. Active ingredient for regenerating the sensory cells of the inner ear, characterized in the it is in a position to at least partly inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear.

50. Active ingredient according to claim 49, characterized in that the cell cycle inhibitor is a cyclin-dependent kinase inhibitor.

51. Active ingredient according to claim 49, characterized in that it is at least one peptide or at least one protein.

52. Active ingredient according to claim 49, characterized in that it is a least one nucleic acid molecule.

53. Active ingredient according to claim 52, characterized in that the nucleic acid molecule is selected from the group consisting of a DNA molecule, cDNA molecule or RNA molecule.

54. Active ingredient according to claim 49, characterized in that the active ingredient is in the form of a vector or vehicle.

55. Pharmaceutical composition or medicament, characterized in that it contains at least one active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear in an active quantity and a pharmaceutically acceptable carrier.

56. Pharmaceutical composition or medicament according to claim 55, characterized in that the active ingredient is an active ingredient according to claim 50.

57. Process according to claim 37 wherein said nucleic acid molecule is recombined nucleic acid molecule.

58. Process according to claim 42 wherein said vector carries a nucleic acid molecule.

59. Active ingredient according to claim 49 wherein the sensory cells regenerated are hair sensory cells.

60. Active ingredient according to claim 50 wherein said cyclin-dependent kinase inhibitor is $p27^{kip1}$.

61. Active ingredient according to claim 52 wherein said nucleic molecule is a recombined nucleic acid molecule

REMARKS

The above amendments have been made in order to prosecute the application on the basis of the original claims and to remove multiple dependencies from those claims. No new matter has been added.

Respectfully submitted,

NATH & ASSOCIATES PLLC

By: _____

Gary M. Nath
Registration No. 26,965
Jerald L. Meyer
Regiatration No. 41,194
Customer No. 20529

Date: August 22, 20000
NATH & ASSOCIATES
1030th Street, NW - 6th Floor
Washington, D.C. 20005
GMN/JLM/dd:AMENDpremPCT

#PRT
09/622719
1 534 Rec'd PCT/PTO 22 AUG 2000

PROCESS FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR

DESCRIPTION

The invention firstly relates to a process for the treatment of diseases or disorders of the inner ear, which are linked with damage or destruction of the sensory cells of the inner ear.

The inner ear of humans and other mammals can either be irreversibly damaged from the outset by a genetic defect or subsequently by external influences. These external influences can e.g. be acoustic trauma or toxic or hypoxic influences. Such damage can lead to functional disturbances or losses of the senses located in the inner ear, particularly hearing. In the case of these functional disturbances particular reference must be made to a reduction or disappearance of the power of hearing. It is estimated that in Germany approximately 12 million people suffer from a so-called perceptive deafness, which can be attributed to the aforementioned pathogenetic mechanisms. Apart from the degeneration of sensory neurons and damage to the so-called stria vascularis of the inner ear, a cause of partial or complete loss of the power of hearing can in particular be damage or destruction of the sensory cells of the inner ear and consequently the hearing organ.

In a process for the treatment of diseases or disorders of the inner ear linked with damage or destruction of the sensory cells, it must be borne in mind that it is no longer possible to regenerate irreversibly damaged and therefore lost cells in the highly differentiated sensory epithelia in the inner ear of humans and other mammals. Thus, a partial or complete hearing loss due to damage or destruction of the sensory cells of the inner ear is generally irreversible. In this respect the sensory epithelia of the inner ear fundamentally differ from other tissues, where necrotic cells can be rapidly replaced by the division of substitute cells and their subsequent maturation.

It is of interest that in other vertebrate classes, such as e.g. birds, necrotic sensory cells in the inner ear can be regenerated, unlike the situation with humans. In birds sensory cells which have died after damage are replaced by so-called supporting cells located in the epithelium below the sensory cells. This takes place by division of the supporting cells and subsequent maturation, a new supporting cell and a sensory cell resulting from a supporting cell.

The discovery of the regeneration of sensory cells in the cochlea of the bird has over the past few years led to an attempt being made to transfer research results made on the bird to mammals and therefore ultimately humans. This inter alia promised success, because the cochlea of the bird and the cochlea

of mammals have cell-biological points in common. Both the sensory epithelium of bird cochlea and the sensor epithelium of mammal cochlea are postmitotic, i.e. sensory cells present in the sensory epithelia are formed only during a specific time period of embryonic development, after which normally no further cell divisions occur. However, this fundamental point in common makes it difficult to understand the phenomenon that in the vestibular sensory epithelium of the bird cell divisions can be detected throughout its life, but not in humans.

As it was recognized in the bird that so-called growth factors can give rise to an increased proliferation rate in the bird cochlea, such growth factors were also used in the mammal cochlea. However, it was not possible to prove a reproducible action. This makes it obvious to draw the conclusion that despite fundamental cell-biological points in common, there must be other significant differences between bird and mammal cochlea. These could be that the supporting cells of the bird cochlea, as in the mammal, are postmitotic, but have only temporarily left the cell cycle. They can then reenter the cell cycle when a corresponding signal appears. Such supporting cells can be called quiescent, i.e. they are in the waiting state. As opposed to this the supporting cells of the mammal pass through a very high and specific differentiation and consequently irreversibly leave the cell cycle. They can consequently be called terminally differentiated and are e.g. comparable with neurons. This can apply in the case of the supporting cells of the mammal, which are referred to as so-called Pillar's or Deiter's cells. Such explanation models for cell-biological differences between bird and mammal cochlea have given rise to a more detailed investigation of the regeneration of the sensory cells in the bird in order to subsequently transfer the results obtained to mammals.

However, the problem of the present invention is to find a new starting point for the treatment of disorders or diseases of the inner ear, which are linked with damage or destruction of the sensory cells of the inner ear. The aim is less to transfer to mammals and in particular humans results obtained on vertebrates other than mammals and more to make available an action mechanism and corresponding active ingredients, which act directly in the cellular processes in the mammal and ultimately lead to a regeneration of the sensory cells of the inner ear.

This problem is solved by the process having the features of claim 1 and the process with the features of claims 2 and 3. Preferred developments are described in the dependent claims 4 to 21. Thus, by reference, the content of all the claims is made into part of the present description.

According to the invention, the process of the aforementioned type is

characterized in that at least one so-called cell cycle inhibitor present in the inner ear has its inhibiting action partly inhibited or eliminated by at least one active ingredient, which results in a regeneration of the sensory cells of the inner ear. From the patent law sense this process also incorporates the use of an active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear, either directly for the treatment of diseases or disorders of the inner ear or indirectly for preparing a pharmaceutical composition or a medicament for the treatment of diseases or disorders of the inner ear, said diseases/disorders being linked with damage or destruction of the sensory cells of the inner ear.

The regeneration of the sensory cells of the inner ear resulting from the process according to the invention preferably takes place through a stimulation of the proliferation of the supporting cells of the inner ear, i.e. the supporting cells also present in the sensory epithelium and usually located between and below the sensory cells. As there are one or more cell cycle inhibitors in the supporting cells of the inner ear, by inhibiting or eliminating their inhibiting action by a suitable active ingredient it is possible to initiate the cell division of the supporting cells, thereby creating a fundamental prerequisite for creating replacement or substitute cells for the necrotic or dead sensory cells. The cells resulting from the division of the supporting cells can then at least partly mature to functional sensory cells.

With regards to the sensory cells of the inner ear referred to up to now, these are preferably so-called hair sensory cells or short hair cells, which have at their upper end hair-like extensions, so-called stereocilia or small sensory hairs. These hair cells are located on the basilar membrane in the so-called corti-organ and form as so-called outer and inner hair cells the actual receptor cells for acoustic transduction in the inner ear. Both the inner and the outer hair cells are of interest for regeneration, regeneration of the outer hair cells representing a particular field of use of the invention as a result of their greater sensitivity. Those supporting cells which are anatomically particularly well associated with the inner or outer hair sensory cells can in particular be used for the active ingredient employed according to the invention. Thus, apart from outer hair sensory cells as supporting cells can be used the so-called Hensen's cells and, below the outer hair sensory cells, the so-called Deiter's cells and "outer" Pillar's cells. These Hensen's, Deiter's and outer Pillar's cells are consequently particularly suitable as replacement cells for the outer hair sensory cells. Correspondingly alongside and below the inner hair sensory cells are provided the so-called inner sulcus cells as supporting cells and within the inner hair sensory cells also the inner Pillar's cells, both being usable as replacement cells for the inner hair sensory cells. Thus, optionally a regeneration of inner or outer hair cells can be selectively initiated

and influenced. Reference can be made in this connection to the relevant textbooks and articles concerning the hearing process in mammals, particularly humans. The regeneration of the hair sensory cells participating in acoustic transduction in the inner ear for the treatment of perceptive deafness in the case of damage to said sensory cells represents the main field of use of the present invention.

The cell cycle inhibitors, whose inhibiting action is to be inhibited or eliminated according to the invention, can fundamentally be different physiological substances, particularly proteins, preventing the cell passing through the normal cell cycle, including cell division. They are preferably so-called cyclin-dependent kinase inhibitors (CDKIs). It is known that during the development of an organism they are expressed to a reinforced extent during the occurrence of terminally differentiated cells and in this way prevent the reentry of the cell into the cell cycle. This would also explain the loss of the dividability of such cells with reinforced expression of cyclin-dependent kinase inhibitors. Cell cycle inhibitors and in particular cyclin-dependent kinase inhibitors of the so-called CIP/KIP family can be selectively expressed in specific cell types. Preferred cyclin-dependent kinase inhibitors are in particular the proteins referred to as $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$. According to the invention preference is given to the cyclin-dependent kinase inhibitor $p27^{Kip1}$. As a result of the selective expression of such inhibitors and the different expression patterns resulting therefrom, the invention can be used for selectively influencing the cell cycle in a specific cell type. If e.g. in a specific cell type, such as e.g. the supporting cells in the sensory epithelium of the inner ear, $p27^{Kip1}$ is expressed selectively or at least with a significant proportion, by means of an active ingredient aimed specifically at this inhibitor, it is possible to eliminate its inhibiting action and consequently initiate or stimulate the proliferation of supporting cells. By means of a maturation of at least part of the cells resulting from the division of the supporting cells, a regeneration of the sensory cells is brought about.

As is apparent from the statements up to now, according to the invention the inner ear disease or disorder involved is in particular a so-called perceptive deafness. This is linked with the already described damage or destruction of the hair sensory cells in the inner ear.

In the case of the active ingredient usable according to the invention, which inhibits or eliminates the inhibiting action of the cell cycle inhibitor, is preferably a substance, which normally acts in intracellular manner either directly or indirectly on the inhibitor, i.e. normally a peptide or protein. The active ingredient is preferably present in the form of a peptide or protein, which effects a peptide-peptide or protein-protein interaction with

the inhibitor. This would then be the case of a "direct" influencing of the function of the inhibitor. If the active ingredient is constituted by a nucleic acid molecule, which codes one of the aforementioned peptides/ proteins for the amino acid sequence, it is possible to refer to an "indirect" influencing, because initially the coding nucleic acid molecule is introduced into the corresponding cell and subsequently the peptide/protein molecule (serving directly as the active ingredient) is expressed. Said nucleic acid molecule can in particular be a recombined nucleic acid molecule. The nucleic acid molecule can fundamentally be a DNA molecule, a cDNA molecule or a RNA molecule.

Another active ingredient usable in preferred manner according to the invention is a nucleic acid molecule, where use is made of the so-called antisense method. In this method which is fundamentally known to the expert use is normally made of a RNA, which is complimentary to the RNA of the normal (physiological) gene. This complimentary RNA is called antisense-RNA. The antisense-RNA can prevent the synthesis of the protein product belonging to the gene. In the case of the invention this means that a nucleic acid molecule, e.g. the antisense-RNA itself or DNA, during whose transcription the antisense-RNA is formed, is introduced into the organism or cell for inhibiting or eliminating the inhibiting action of the cell cycle inhibitor. This introduction preferably takes place with the aid of lipid compounds, which also carry viral components for the better docking and penetration of the nucleic acid molecule into the cell.

As stated, the active ingredient in the case of the invention can effect a direct interaction, preferably a peptide-peptide or protein-protein interaction with the cell cycle inhibitor. However, the active ingredient can also indirectly inhibit or eliminate the inhibiting action of the cell cycle inhibitor, in that it interacts at least as well or preferably better with a physiological interaction partner of the cell cycle inhibitor than the cell cycle inhibitor itself. This prevents the cell cycle inhibitor from evolving its physiological (inhibiting) action.

Thus, e.g. in the case of the cyclin-dependent kinase inhibitor $p27^{Kip1}$, it is known that it forms a protein complex together with the cyclin-dependent kinase CDK2 and cyclin A. There are specific points at which peptide-peptide interactions occur between the $p27^{Kip1}$ and the CDK2 or cyclin A. Thus, e.g. identification has taken place of a bonding point of very high affinity between $p27^{Kip1}$ and cyclin A and several less strong bonding points between $p27^{Kip1}$ and cyclin A or $p27^{Kip1}$ and CDK2. On extracting one of the bonding points where there is no high or very high affinity bonding/interaction, an active ingredient, preferably in the form of a further peptide/protein can be selected or developed can effect a bonding/interaction of at least as high or

preferably higher affinity with one of the two interaction partners at the particular bonding point. This inhibits or prevents the standard physiological interaction, because the corresponding bonding point for the physiological interaction partner is blocked.

Thus, e.g. for a bonding point between $p27^{Kip1}$ and cyclin A, but also CDK2, an optimized peptide structure or optimized amino acid sequence can be developed for the amino acid sequence of $p27^{Kip1}$ at this point, which then bonds with a better, i.e. higher affinity with the corresponding sequence of cyclin A or CDK2 at this point. Such an optimized peptide structure e.g. and preferably comprises up to 15 amino acids and can then be directly introduced into the cell or preferably expressed in intracellular manner by an artificially introduced gene. Through the high affinity of such a peptide the interaction of the physiological peptide partner is then destroyed and the formation of the peptide complex, based on the inhibiting action of the cell cycle inhibitor is prevented. Thus, the active ingredient ensures an at least partial inhibition or a complete elimination of the inhibiting action of the cell cycle inhibitor. As a result of this process starting point of the invention the concentration of the active ingredient, particularly the peptide/protein with the corresponding amino acid sequence in the cell only has to be roughly of the same level as the corresponding concentration of the cell cycle inhibitor, whose action is to be inhibited or eliminated. As such concentrations, e.g. of $p27^{Kip1}$ are approximately 10 nM/l and roughly correspond to 1,000 to 10,000 molecules per cell, even very low concentrations can suffice for the performance of the invention. It is also important that for achieving such a concentration using gene-therapeutic methods it is sufficient to introduce only a single copy of a DNA, coding for the corresponding amino acid sequence, for each cell. Compared with other methods which have to use much higher concentrations or a larger number of DNA copies, this represents a decisive advantage.

According to a further development the process according to the invention can be performed in such a way that the active ingredient is in the form of a so-called vector or vehicle, said vector or vehicle carrying at least one of the above-described nucleic acid molecules. Preferably it is a nucleic acid molecule, which codes for the amino acid sequence of a peptide or protein serving as the active ingredient. Said vectors can be conventional viral and non-viral vectors, as are known to the expert. When using viral vectors use can be made of retroviruses, adenoviruses or adeno-associated viruses. In the case of non-viral vectors it is known that no viral DNA participates, so that here fundamentally a "bare" DNA can be introduced into a cell. However, preferably such nucleic acid molecules are packed in so-called liposomes or lipoplexes and are introduced in this form into the organism and cell. The use of non-viral vectors or lipoplexes is fundamentally preferred, because

viral vectors have certain disadvantages known to the expert. As a result of the above-described use possibilities of the invention, it is here frequently possible to operate without using viral vectors, because the effectiveness of the active ingredients used is very high and it is correspondingly possible to operate with low concentrations.

In the invention the active ingredient used is preferably employed in a therapeutically active quantity. In the conventional manner this can be matched to the subject undergoing treatment and inter alia use can be made of known pharmaceutical additives. According to a further development the active ingredient used and correspondingly also the process according to the invention can be provided for local application. This makes it possible to avoid possible disadvantages of a systemic application. The target location of the process according to the invention, namely the inner ear, is particularly suitable for local application. Thus, in the present case the active ingredient can be introduced into the so-called perilymphatic space of the inner ear of the mammal, particularly human. This is a small liquid space with a very slow exchange rate, which is accessible to therapeutic intervention from the middle ear, e.g. via the membrane of the circular window. This perilymphatic space has a volume of only approximately 20 microlitres and is also in direct contact with the cells of the corti-organ. This ensures a direct action of the active ingredient on the sensory epithelium with its hair cells and supporting cells.

The invention also relates to the actual active ingredient, whose use is described in detail in the above-described process. Reference is made to the content and wording of claims 22 to 27. This active ingredient is intended for the regeneration of the sensory cells of the inner ear, particularly the hair sensory cells of the inner ear and is able to at least partly inhibit or eliminate the inhibiting action of a so-called cell cycle inhibitor present in the inner ear. The cell cycle inhibitor is preferably a cyclin-dependent kinase inhibitor, particularly the cyclin-dependent kinase inhibitor $p27^{Kip1}$. Reference is made to the statements hereinbefore concerning the specific, preferred characteristics of the active ingredient. As stated, it can be at least one peptide/protein or at least one nucleic acid molecule, the latter preferably being an antisense-DNA or antisense-RNA or preferably codes for a corresponding peptide/protein usable as the active ingredient. The nucleic acid molecule can be a DNA molecule, a cDNA molecule or a RNA molecule. In particular, the nucleic acid molecule is introduced with the aid of a suitable vector or vehicle into the organism or cell and these can be the described viral or non-viral vectors or nucleic acid molecules packed in liposomes/lipoplexes.

The invention finally relates to a pharmaceutical composition or medicament, which contains at least one active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear, in an active quantity, as well as conventionally a pharmaceutically acceptable carrier or support. With respect to the active ingredient contained in the composition or medicament express reference is made to the statements hereinbefore and the content of claims 28 and 29.

The described and further features of the invention can be gathered from the following description of a preferred embodiment in conjunction with the subclaims, the example and the drawing. The individual features can be implemented individually or in the form of subcombinations.

Fig. 1 is an electron micrograph of a cell in nuclear division in the sensory epithelium of the corti-organ of a so-called $p27^{Kip1}$ knockout mouse.

Example

For the test use was made of a so-called $p27^{Kip1}$ knockout mouse (p27-/-), a mouse lacking the gene for expressing the protein $p27^{Kip1}$. Thus, in such a mouse $p27^{Kip1}$ cannot evolve per se its cell cycle-inhibiting action.

The corti-organ is removed from such a $p27^{Kip1}$ knockout mouse on the seventh day after birth (postnatal day 7) and is prepared in the usual way for electron microscopic examination making it possible to see the sensory epithelium of the corti-organ.

The result of the electron microscopic examination is shown in fig. 1. This electronic micrograph shows that a cell in nuclear division (mitosis), i.e. a mitotic cell is located between two left-hand, upper or right-hand, lower, inner hair cells, whereof the black bordered nuclei are at the left-hand top (complete) and right-hand bottom (partial). Mitosis is clearly visible on the condensed chromatin, the dissolved nuclear membrane and the basal body. the inner hair cell top left and the basal body are given English-language captions in the drawing to facilitate understanding.

Fig. 1 clearly shows that the lack of the cell cycle inhibitor $p27^{Kip1}$ leads to the possibility of a cell division of supporting cells located there in the sensory epithelium of the corti-organ of the mouse. Mention is also made of the fact that in the case of the cell division shown in fig. 1 it is not a single phenomenon within the sensory epithelium of the corti-organ, but instead a large number of the cells there undergo a cell division and therefore pass through the cell cycle. The phenomenon shown in fig. 1

enables the conclusion to be drawn that not only a cell division, but also following a cell division, which represents the decisive step in the hair cell regeneration process, there is also a differentiation or maturation to hair sensory cells and finally a functional recovery of the auditory function of the sensory organ. Thus, a regeneration of the sensory cells is possible. This conclusion is supported by the fact that in the case of the knockout mouse there is not a single mitosis, but instead such knockout mice have more hair cells than normal mice, in which the protein $p27^{Kip1}$ is expressed. Thus, the mitosis of the supporting cells also results in matured sensory cells. The correctness of this conclusion is confirmed by the following results. In the case of heterozygous knockout mice the regeneration of hair cells was proved in that in the second week of living of the animals when they evolve the auditory function, the hair cells were destroyed by the systemic administration of amikacin. After a further two weeks without any injection the animals were killed and their cochlea examined. This revealed regenerated hair cells in the cochlea, which are marked or labelled by a proliferation marker or label (bromodesoxyuridine - BrdU) e.g. administered with the amikacin.

Thus, not only in knockout mice where the gene for $p27^{Kip1}$ was missing from the outset, but also by inhibiting or eliminating the $p27^{Kip1}$ expressed in the normal organism, e.g. with the aid of a peptide interacting with $p27^{Kip1}$ or one of its physiological partners, with the aid of the nucleic acid sequence coding for this peptide or with the aid of an antisense-DNA/antisense-RNA it is possible to bring about a regeneration of the sensory cells. This can also take place by an only partial elimination of the function of $p27^{Kip1}$, because in the case of heterozygous mice a gene dose-dependent effect is observed.

ART 34 AMDT

CLAIMS

1. Process for the treatment of diseases or disorders of the inner ear linked with damage or destruction of the sensory cells of the inner ear, characterized in that for the regeneration of the sensory cells of the inner ear the inhibiting action of at least one cell cycle inhibitor present in the inner ear is at least partly inhibited or eliminated by an active ingredient.

2. Use of an active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear, for the treatment of diseases or disorders of the inner ear linked with damage or destruction of the sensory cells of the inner ear.

3. Use of an active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear, for the preparation of a pharmaceutical composition or a medicament for the treatment of diseases or disorders of the inner ear linked with damage or destruction of the sensory cells of the inner ear.

4. Process or use according to one of the preceding claims, characterized in that the regeneration of the sensory cells of the inner ear takes place by stimulating proliferation of the supporting cells of the inner ear.

5. Process or use according to one of the preceding claims, characterized in that the sensory cells of the inner ear are hair sensory cells.

6. Process or use according to one of the preceding claims, characterized in that the cell cycle inhibitor is a cyclin-dependent kinase inhibitor.

7. Process or use according to claim 6, characterized in that the cyclin-dependent kinase inhibitor is the cyclin-dependent kinase inhibitor $p27^{Kip1}$.

8. Process or use according to one of the preceding claims, characterized in that the disease or disorder of the inner ear is a perceptive deafness.

9. Process or use according to one of the preceding claims, characterized in that the active ingredient is at least one peptide or at least one protein.

10. Process or use according to one of the preceding claims, characterized in that the active ingredient is at least one nucleic acid molecule, particularly recombined nucleic acid molecule.

Amended sheet

11. Process or use according to claim 10, characterized in that the nucleic acid molecule codes for a peptide or a protein according to claim 9.

12. Process or use according to claim 10 or 11, characterized in that the nucleic acid molecule is a DNA molecule.

13. Process or use according to claim 12, characterized in that the nucleic acid molecule is a cDNA molecule.

14. Process or use according to claim 10 or 11, characterized in that the nucleic acid molecule is a RNA molecule.

15. Process for the treatment of diseases or disorders of the inner ear linked with damage or destruction of the sensory cells of the inner ear, characterized in that for regenerating the sensory cells of the inner ear the inhibiting action of a cyclin-dependent kinase inhibitor present in the inner ear is at least partly inhibited or eliminated by an active ingredient.

16. Process according to claim 15, characterized in that the cyclin-dependent kinase inhibitor is the cyclin-dependent kinase inhibitor $p27^{Kip1}$.

17. Process according to claim 15 or 16, characterized in that the active ingredient is at least one nucleic acid molecule, particularly recombined nucleic acid molecule.

18. Process according to claim 17, characterized in that the nucleic acid molecule is a RNA molecule.

19. Process according to claim 17 or 18, characterized in that the nucleic acid molecule is an antisense sequence.

20. Process or use according to one of the preceding claims, characterized in that the active ingredient is in the form of a vector and the vector preferably carries a nucleic acid molecule according to one of the claims 10 to 14.

21. Process or use according to claim 20, characterized in that the vector is a viral vector.

22. Process or use according to claim 21, characterized in that the virus is a retrovirus, an adenovirus or an adeno-associated virus.

23. Process or use according to claim 20, characterized in that the vector is a non-viral vector.

24. Process or use according to one of the claims 10 to 14, characterized in that it is a nucleic acid molecule packed in a liposome or a lipoplex.

25. Process or use according to one of the preceding claims, characterized in that the active ingredient is used in a therapeutically active quantity.

26. Process or use according to one of the preceding claims, characterized in that the active ingredient is intended for local application.

27. Pharmaceutical composition or medicament, characterized in that it contains at least one active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor, particularly a cyclin-dependent kinase inhibitor present in the inner ear in an active quantity and a pharmaceutically acceptable carrier.

BEST AVAILABLE COPY

PROCESS FOR THE TREATMENT OF DISEASES OR DISORDERS OF THE INNER EAR

ABSTRACT

In a process for the treatment of diseases or disorders of the inner ear linked with damage or destruction of sensory cells of the inner ear, for regenerating the sensory cells use is made of at least one active ingredient, which at least partly inhibits or eliminates the inhibiting action of at least one cell cycle inhibitor present in the inner ear. In this process the sensory cells of the inner ear are preferably regenerated by stimulating the proliferation of supporting cells. The sensory cells of the inner ear are so-called hair sensory cells. As cell cycle inhibitors use can be made of cyclin-dependent kinase inhibitors such as in particular the cyclin-dependent kinase inhibitor $p27^{Kip1}$.

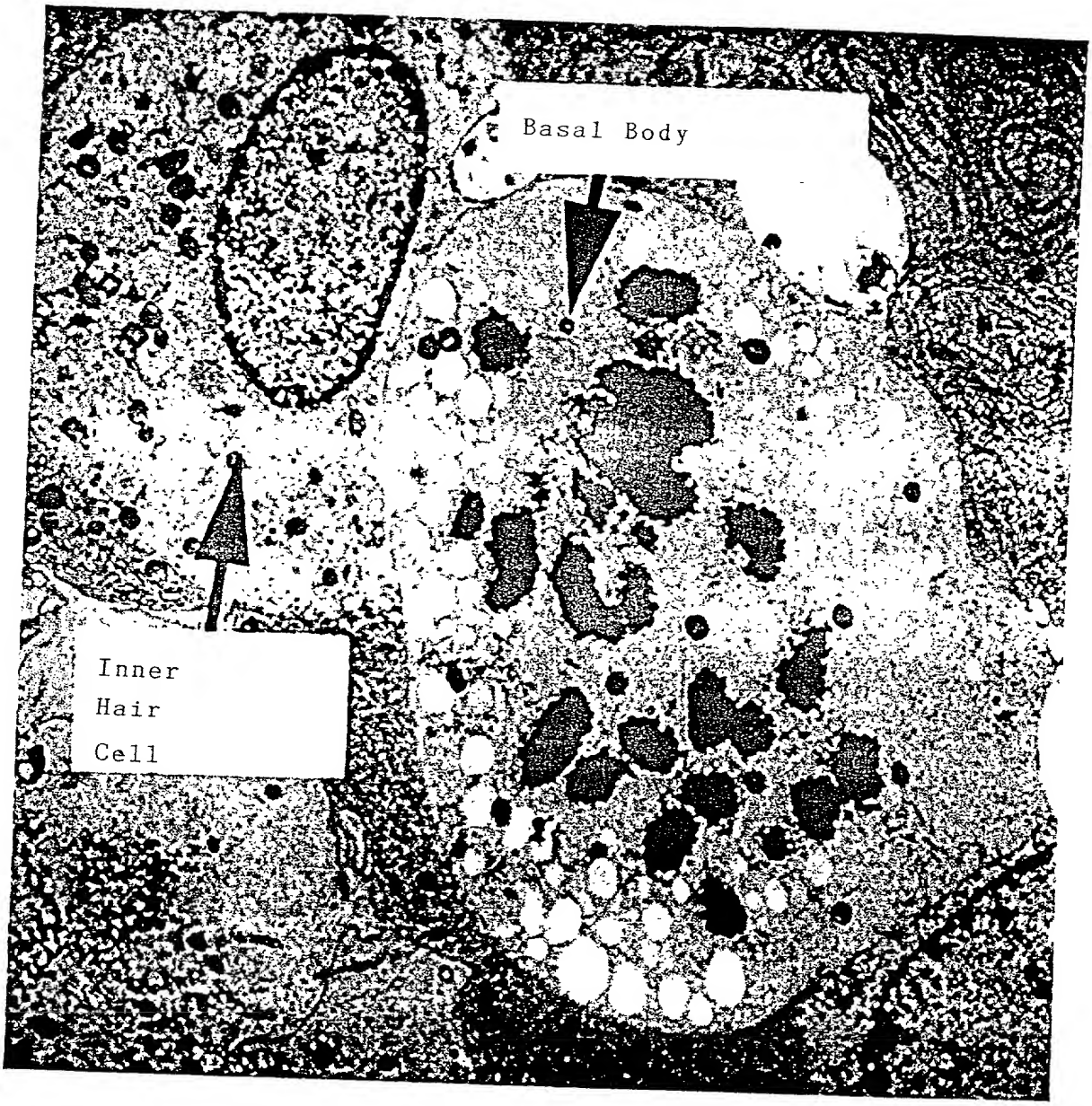

Fig. 1

#3

A 35 223 PCT/US

DECLARATION FOR PATENT APPLICATION	Attorney Docket: 24356

As a below-named inventor(s), I/we hereby declare that:

My/Our residence(s), post office address(es) and citizenship(s) is/are as stated below next to my/our name(s).

I/We believe I/we am/are the original inventor, first and sole (*if only one name is listed below*) or the original, first and joint inventors (*if plural names are listed below*) of the subject matter which is claimed, and for which a patent is sought on the invention entitled: Method for the treatment of diseases or disorders of the inner ear
the specification of which: (check one)

[ ] is attached hereto.

[X] was filed on 23 February 1999 as Serial No. PCT/EP99/01153
22 August 2000 09/622,719

and was amended on _____ (if applicable).

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the patentability of this application as defined by 37 CFR § 1.56.

We hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Applications:

(Application No.)	(Country)	(Day/Month/Year Filed)	Priority Claimed [X] Yes	[ ] No
198 07 426.3	Germany	23 /02 / 1998	[X]	[ ]
		/ /	[ ]	[ ]
		/ /	[ ]	[ ]

14

We hereby appoint Gary M. Nath, Reg. No. 26,965; Harold L. Novick, Reg. No. 26,011; Suet M. Chong, Reg. No. 38,104; Todd L. Juneau, Reg. No. 40,669; Patricia M. Drost, Reg. No. 29,790; Lee C. Heiman, Reg. No. 41,827; Jerald L. Meyer, Reg. No. 41,194; Josnua B. Goldberg, Reg. No. 44,126; David Milligan, Reg. No. 42,893 and Robert G. Lev, Reg. No. 30,280; David R. Murphy, Reg. No. 22,751; Paul A. Sacher, Reg. No. 43,428; Gregory B. Kang, Reg. No. P-45,273; Scott F. Yarnell, P-45,245; as my attorneys to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith.

Direct Telephone Calls to:

Gary M Nath
(202) 775-8383

Send Correspondence to:
NATH & ASSOCIATES
Sixth Floor
1030 15th Street, N.W.
Washington, D.C. 20005 U.S.A.

We hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by 35 U.S.C. § 112, first paragraph, I/we acknowledge the duty to disclose material information as defined in 37 CFR § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. Application Serial No.)	(U.S. Filing Date)	(Status--patented, pending, abandoned)

DECLARATION FOR PATENT APPLICATION	Attorney Docket: 24356

We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and furtner that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

Full name of sole or first inventor: Hubert LOEWENHEIM

Inventor's Signature Hubert Löwenheim Date 23.08.2000

Residence: D-72076 Tuebingen, Germany DE

Country of Citizenship: Germany

Post Office Address: Philipp-von-Heck-Strasse 1, D-72076 Tuebingen, Germany

Full name of second inventor: _____

Inventor's Signature _____ Date _____

Residence: _____

Country of Citizenship: _____

Post Office Address: _____

Full name of third inventor: _____

Inventor's Signature _____ Date _____

Residence: _____

Country of Citizenship: _____

Post Office Address: _____

Full name of fourth inventor: _____

Inventor's Signature _____ Date _____

Residence: _____

Country of Citizenship: _____

Post Office Address: _____

D E C L A R A T I O N

I, JOHN ALFRED RICHES, Fellow of the Institute of Linguists, of Oak Farm, Catfield, Great Yarmouth, Norfolk, England, do hereby declare that I am conversant with the English and German languages and am a competent translator thereof. I declare further that the following is a true and correct translation made by me of patent application PCT/EP99/01153 (amended pages only) in the German language attached hereto.

Signed this 15th day of August, 2000.

D E C L A R A T I O N

I, JOHN ALFRED RICHES, Fellow of the Institute of Linguists, of Oak Farm, Catfield, Great Yarmouth, Norfolk, England, do hereby declare that I am conversant with the English and German languages and am a competent translator thereof. I declare further that to the best of my knowledge and belief the following is a true and correct translation made by me of internation patent application PCT/EP99/01153 (amended pages only).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this fifteenth day of August, 2000.